

REMARKS

Status of the Claims

Claims 1 and 7 are pending. Claims 1 and 7 are rejected. Claim 1 is amended herein. Claims 2-6 and 8-22 are canceled. No new matter has been added.

Claim amendments

Claim 1 is amended to recite that the high specific activity of the bismuth-213/antibody construct is about 20 mCi/mg to about 30 mCi/mg. This amendment is supported by the specification on page 29, lines 6-10 as well as Figure 3A. Claim 1 also is amended to recite that the selected dose of the construct provides a pharmacologically effective amount of antibody to “saturate” the targeted binding sites on the outer layer of cells. This amendment is supported by the specification on page 12, lines 2-3. In addition claim 1 is amended to recite that at saturation “more than two atoms” of Bi-213 deliver at least one alpha to each targeted cell. This amendment is supported by the specification on page 29, lines 23-26.

The 35 U.S.C. §103(a) rejection

Claims 1 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson et al.** (1990, Can. Res., 50(3 Supp:9855-9885) in view of **Kasperson et al.** (1995, Nuclear Med Comm, 16:468-476), **Vieira et al.**

(1996, Eur J Surgical Oncology, 22(4):331-4), and **Blankenberg et al.** (U.S. Patent No. 6,197,278), and further in view of **Goldenberg** (U.S. Patent No. 4,444,744), all of record. Applicants respectfully traverse this rejection.

In considering independent claim 1, the Examiner states that **Simonson et al.** teach the i.p. administration of 212-Bi labeled antibodies specific for mucin antigen TAG-72 to mice injected with LS1744T cells, which grows as solid tumors and ascites therein and in which solid tumors developed followed by ascites at about 20 days after injection of tumor cells (pg. 985s, 2nd col., last PP; pg. 987s, 2nd col., 1st PP). The Examiner also states that **Simonson et al.** disclose that the specific activity of labeled antibody is 5 to 10 mCi/mg (pg. 986s, 1st col, 2nd PP). In addition the Examiner states that **Simonson et al.** discloses that the tumor averages 3 gm at 13 days (Fig. 1) and that with single and repeated administration of Bi-212-antibody, 56% decrease in tumor mass is obtained (pg. 986s, 1st col., 3rd PP; Fig. 1). The Examiner further states that efficacy would be better if the antibody recognized a cell surface antigen rather than the secreted mucin antigen TAG-72 (pg. 987s, 2nd col.).

The Examiner also states that **Simonson et al.** do not teach a method of killing a tumor greater than 1 mm in size by intravenously administering Bi-213 labeled antibodies at a dose adequate to deliver a minimum of 1 alpha track per cell. As such, the Examiner contends that although no specific teaching is found in **Simonson et al.** that the treated tumors are at least 1 mm in size, the tumor at 13 days weighs an average of 3 gm would be at least that size. Also, the Examiner states that **Kaspersen et al.** teach that Bi-213 is an alternative to Bi-

212 with the advantage of safer and easier production (pg. 475, 1st col., 1st PP). The Examiner states that **Vieira et al.** teach that imaging of breast cancer tissues could begin 10 minutes after intravenous administration of radiolabeled monoclonal antibodies (Abstract, pg. 332, 3rd PP). The Examiner states that **Blankenberg et al.** teach that localization of an intravenously administered targeting protein, i.e., annexin which has high affinity for anionic phospholipid surface in the target tissue, can be obtained in only a few minutes (col. 9-10). The Examiner states that **Goldenberg** teaches the use of radiolabeled antibodies to cancer cell surface antigens for cancer immunotherapy.

Thus, the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to substitute Bi-212 with Bi-213 and to use an antibody that targets a membrane specific antigen on cancer cells which have been successfully used in the art, as taught by **Kaspersen et al.** and **Blankenberg et al.**, respectively, in the method of treating cancer in **Simonson et al.** The Examiner also concludes it would have been obvious to an ordinary practitioner to administer the Bi-213-antibody intravenously one or more times, as taught by **Simonson et al.**, as a convenient, alternative and routine route of administration for immunotherapy because **Vieira et al.** and **Blankenberg et al.** teach that radiolabeled targeting compounds, including radiolabeled antibodies, reach the target cells within minutes after intravenous administration. The Examiner also concludes that one of ordinary skill in the art would be motivated to treat tumors at least 1 mm in size using a Bi-213 labeled antibody that targets a

specific binding site on tumor cells with a reasonable expectation of success. Applicants respectfully disagree.

Applicants respectfully submit that **Simonson et al.** teach that Bi-212 may be appropriate for the treatment of peritoneal implant metastases and ascitic cancer when administered intraperitoneally as demonstrated with a Bi-212 labeled B72.3 antibody against the human colon carcinoma cell line LS174T in a murine model is examined (pg. 985s, first col., last paragraph to second col., second paragraph). The specific activity of the labeled antibody was 5-10 $\mu\text{Ci}/\mu\text{g}$. **Simonson et al.** demonstrate that a single i.p. injection of 450 μCi or 3 consecutive i.p. injections of 190 μCi 13 days after tumor inoculation reduced tumor mass by 56% of well-advanced tumors averaging 3 gms in weight (pg. 986s, first col., third paragraph). In a model using smaller tumors four consecutive i.p. doses starting at day 8 of either 90 μCi or 180 μCi reduced tumor mass on average 85% with all mice in any regimen demonstrating some toxicity (pg. 986s, first col., fifth paragraph).

Kasperson et al. examined the cytotoxicity of Bi-213 *in vitro* and Ac-225 immunoconjugates against the human carcinoma cell lines A431 and SW1398. Bi-23 radioimmunoconjugates with a limited specific activity of 3 $\mu\text{Ci}/\mu\text{g}$ were prepared (pg. 472, 1st col., last PP). In an *in vivo* spheroid model of SW1398 cells no specific cell-killing was observed using up to 1.2 μCi Bi-213 on spheroids with diameters of 0.4 mm to 0.7 mm (pg. 474, 2nd col., ll. 6-9). **Kasperson et al.** state that Bi-213 may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph). The reference discloses that Bi-²¹³ may

be substituted for Bi-212 for the treatment of single cell malignancies (pg. 475, col. 1, line 3).

Vieira et al. teach the use of 99mTc-tetrofosmin as a gamma ray imaging agent to differentiate benign from malignant lesions in breast tissue. Imaging commences 10 minutes after injection (Abstract). However, contrary to the Examiner's statement, **Vieira et al.** only state that radiolabeled monoclonal antibodies are an example of a potential imaging agent already under investigation as a means of detecting breast cancer. In the abstract, **Vieira et al.** specifically investigate 99mTc-labeled tetrofosmin, that is 99mTc-ethoxy-ethyl phosphinoethane, which is a lipophilic, cationic chemical compound and not a radiolabeled monoclonal antibody.

Blankenberg et al. teach a method of imaging regions of cell death in a mammal using radiolabeled annexin V for gamma ray imaging (Abstract; col. 1, ll. 12-15). Radiolabeled annexin may be administered intravenously (col. 9, ll. 25-28) and imaging generally begins after most of the radiolabeled annexin V has localized to its target which for i.v. administration is about 30-70 minutes (col. 9, ll. 66 to col. 10, ll. 3). If the target is easily accessible, such as injured blood vessels, localization may take only a few minutes (col. 10, ll. 7-13). Annexin V is not an antibody, but rather a protein isolated from tissue that binds to phosphatidylserines released from or exposed on the cytoplasmic side of cell membranes damaged due to apoptosis or necrosis of the cell.

Goldenberg teaches a method of using antibodies highly specific to cell surface antigens that are radiolabeled for tumor localization and detection or

for tumor therapy (Abstract). The antibodies are preferably labeled with the gamma emitter, I-131, for radiotherapeutic applications, but may be labeled with alpha emitters, preferably Sc-47, or beta emitters (col. 12, ll. 21-34).

The scope of amended claim 1 is to sequentially reduce the size of a tumor at least 1 mm in size using a selected high specific activity, i.e., 20-30 mCi/mg, bismuth-213/tumor specific antibody construct whereby a selected dose of bismuth-213/antibody saturates the targeted binding sites on an outer layer of tumor cells so that more than two atoms of Bi-213 delivers at least one alpha particle to each targeted tumor cell. Sequential removal of layers of tumor cells increase the tumor control probability, and thereby the probability of remission, in individuals having a solid tumor greater than 1 mm.

A determination of obviousness requires a teaching or suggestion of all the claim elements in the combination of cited prior art which provides motivation for one of ordinary skill in the art to make the combination with a concomitant reasonable expectation of success not found in Applicants' specification. Also, the teachings of the cited prior art references must be considered as a whole, including that which teaches away from the claimed invention.

Simonson et al. do not teach or suggest a high specific activity of about 20 mCi/mg to about 30 mCi/mg for the Bi-213/antibody construct. **Simonson et al.** teach that Bi-212 constructs had specific activities of 5-10 $\mu\text{Ci}/\mu\text{g}$, i.e., 5-10 mCi/mg, and disclose that 90-450 mCi were administered intraperitoneally in single or multiple doses. **Simonson et al.** teach that certain

doses of the 5-10 $\mu\text{Ci}/\mu\text{g}$ specific activity Bi-212-GYK-DTPA-B72.3 construct decreased tumor burden and prolonged survival in some mice, although no cures were effected. **Simonson et al.** disclose that the reduced efficacy of the Bi-212-GYK-DTPA-B72.3 construct is due to 1) B72.3 recognizes a secreted rather than cell surface-bound antigen; 2) treatment was not begun until at least 7 days after injection of LS174T cells such that the tumor was well established; and 3) ascites developed after the development of solid LS174T tumor (pg. 987s, 2nd col., 1st PP). Thus, no suggestion to increase specific activity to the high specific activities of about 20 mCi/mg to about 30 mCi/mg as a means to increase the efficacy of Bi-212 is present in **Simonson et al.** and, therefore, no motivation is present for one of ordinary skill in the art to do so. The instant specification teaches that the highest specific activities had the highest selective cell killing and as specific activity decreased so did selectivity (pg. 29, ll. 6-13).

Combining **Kaspersen et al.**, **Vieira et al.**, **Blackenberg et al.** and **Goldenberg** with **Simonson et al.** do not remedy all the deficiencies in **Simonson et al.** In considering **Kaspersen et al.** as a whole, one of ordinary skill in the art would find that **Kaspersen et al.** teach that Bi-213, with its safer, easier production, may be an alternative to Bi-212 for blood-borne or single cell malignancies (Abstract; pg. 475, 1st col., ll. 3-5)) and may have limited applicability for solid tumors (pg. 474, last paragraph). Applicants strongly maintain that **Kaspersen et al.** teach away from treating solid tumors with Bi-213.

Applicants respectfully submit that Bi-212 generators are different from Bi-213 generators. At the time of the instant invention, **Kaspersen et al.**

were limited to specific activities of 3 $\mu\text{Ci}/\mu\text{g}$, i.e., 3 mCi/mg, because of the amount of Bi-213 available. Therefore, one of ordinary skill in the art does not even have a reasonable expectation of success of generating even the 5-10 $\mu\text{Ci}/\mu\text{g}$, i.e., 5-10 mCi/mg, specific activity disclosed in **Simonson et al.** Therefore, no reasonable expectation of success in making an amount of Bi-213 adequate to prepare the high specific activity of about 20 mCi/mg to about 30 mCi/mg Bi-213 antibody construct is present given the disclosure in **Kaspersen et al.** Applicants' specification discloses that the construction of generators capable of producing 10-25 mCi of Bi-213 required several modifications of the generator disclosed in Kaspersen et al. (pg. 23, ll. 27-28).

Nor does combining **Vieira et al.**, **Blackenberg et al.** and **Goldenberg** with **Simonson et al.** and **Kaspersen et al.** provide a teaching or suggestion to remedy the deficiencies in the combination of **Simonson et al.** with **Kaspersen et al.** **Vieira et al.**, **Blackenberg et al.** and **Goldenberg** only disclose that various radiolabeled imaging agents or antibodies can either localize at or specifically bind to various targets within 10 to 70 min of intravenous injection. No teaching or suggestion, not found in Applicants' specification, is present in the combination to make or use an adequate dose of a Bi-213 antibody construct having a high specific activity of about 20 mCi/mg to about 30 mCi/mg, as recited in amended independent claim 1.

In addition, the Examiner stated that determining the dosage of the labeled antibodies recited in claim 1 is within the level of ordinary skill in the art. Applicants strongly disagree. Amended independent claim 1 recites that a dose

of the about 20 mCi/mg to about 30 mCi/mg Bi-213 antibody construct must be selected that is effective to saturate the targeted binding sites so that more than 2 atoms of Bi-213 delivers at least one alpha particle to each targeted tumor cell. The instant specification teaches that a minimum adequate specific activity of the radioactive construct is an integral characteristic of its description. Without this feature described it is not possible for one of ordinary skill in the art to prepare a useful dose (pg. 12, ll. 11-14). The combination of cited references does not provide a suggestion or guidance for constructing applicants Bi-213 antibody/construct with high specific activities of the about 20 mCi/mg to about 30 mCi/mg, or for selecting a saturating dose or that saturation of the targeted sites is required to deliver more than 2 atoms for cell specific killing of the tumor cells comprising the outer layer of the solid tumor.

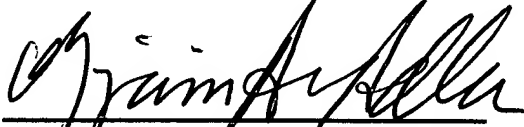
Thus, absent a teaching or suggestion of these claim elements in the combination of **Simonson et al.** with **Kaspersen et al.**, **Vieira et al.**, **Blackenberg et al.** and **Goldenberg**, no motivation is present for one of ordinary skill in the art to make the combination. Therefore, the combination of **Simonson et al.** with **Kaspersen et al.**, **Vieira et al.**, **Blackenberg et al.** and **Goldenberg** cannot render amended independent claim 1 and. Furthermore, claim 7 depends directly from amended independent claim 1. If the combination of **Simonson et al.** with **Kaspersen et al.**, **Vieira et al.**, **Blackenberg et al.** and **Goldenberg** cannot render amended independent claim 1 obvious, then neither is dependent claim 7 rendered obvious by the combination. Accordingly, in view of the claim

amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §103(a), be withdrawn.

Applicants submit that claims 1 and 7, as presented herein, are in condition for allowance. Accordingly, Applicants request that claims 1 and 7 be passed to issuance. This is intended to be a complete response to the Office Action, mailed June 28, 2007. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants enclose a Petition for a Three Month Extension of Time. Please charge the \$525 petition fee to the credit card identified on the enclosed Form PTO-2038. **Only in the absence** of Form PTO-2038, please debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

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